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Tumor Lysis Syndrome Occurring After the Administration of Rituximab in Lymphoproliferative Disorders: High-Grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia

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Rituximab, an anti-CD20 antibody, has been recently approved for the treatment of low-grade or follicular non-Hodgkin's lymphoma (NHL). Because of its relatively benign side effect profile, it has been considered a nontoxic alternative to chemotherapy. Recently, however, tumor lysis syndrome (TLS) resulting from rituximab has been reported in a patient with chronic lymphocytic leukemia (CLL). We herein present two cases of rituximab-induced TLS. The first case occurred in a patient with high-grade NHL, while the second case occurred in a patient with CLL. We also present a summary of the literature regarding TLS induced by immunotherapies. Am. J. Hematol. 62:247–250, 1999.

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Key words: rituximab; IDEC-C2B8; tumor lysis syndrome; immunotherapy; lymphoproliferative disorder; non-Hodgkin's lymphoma; chronic lymphocytic lymphoma; AIDS

INTRODUCTION

Rituximab (Rituxan®, previously known as IDEC-C2B8) is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found primarily on the surface of B-lymphocytes [1,2]. The binding of antibody to CD20 antigen with interaction of human effector cells results in B-cell lysis through antibody-dependent as well as complement-dependent cytotoxicity [3]. Rituximab has been recently approved by the FDA for the treatment of relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma (NHL). It has been considered a nontoxic alternative to chemotherapy regimens because of its relatively benign adverse effect profile [4,5]. Adverse effects usually occur within 30 min to 2 h of drug infusion, are generally limited to the first dose of rituximab, and subside with subsequent doses. Recently, tumor lysis syndrome (TLS) resulting from rituximab therapy has been reported in a patient with chronic lymphocytic leukemia (CLL) [6].

We herein describe two patients with TLS following a single dose of rituximab. The first is an AIDS patient with high-grade NHL who developed TLS with acute renal failure immediately after the first dose. The second is a patient with CLL who developed TLS with severe metabolic acidosis. We also summarize the literature regarding TLS induced by immunotherapies.

CASE ONE

A 42-year-old African American male with a history of AIDS and high-grade small, noncleaved non-Burkitt's lymphoma presented with severe lower back pain secondary to T6 and T7 thoracic vertebral metastasis documented by MRI. He was admitted to UCLA Medical Center to rule out spinal cord compression. He had presented 1½ years before with a right-sided cervical mass. Four cycles of m-BACOD chemotherapy (7) yielded a complete remission. Upon relapse, he was treated with 4 cycles of EPOCH (8) followed by 1 cycle of DHAP (9) complicated by acute renal insufficiency. He received

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radiotherapy for metastatic lesions involving the right mandible, right posterior ribs, and thoracic vertebrae. For HIV he had been treated with multiple antiretroviral agents and pneumocystis prophylaxis. His most recent CD4 count was 107, and viral load was undetectable. Complete blood count on admission revealed: Hb 7.7 g/dl, platelets 40 × 10^9/l, leukocytes 3.8 × 10^9/l, with a differential count of 81% neutrophils, 13% lymphocytes, and 5% monocytes. Blood chemistries showed sodium 135 mmol/l, potassium 3.8 mmol/l, chloride 99 mmol/l, CO_2 24 mmol/l, BUN 13 mg/dl, creatinine 0.8 mg/dl, phosphate 4 mg/dl, magnesium 1.1 mg/dl, and uric acid 5 mg/dl. His ionized calcium was mildly elevated at 1.31 mg/dl (normal 1.09–1.29), and he was treated with pamidronate. His LDH was elevated to 3510 U/l (normal 60–100). Total bilirubin, AST and ALT were normal. The patient received his first dose of rituximab 375 mg/m^2 IV over 2 h on the third day after admission. Serum creatinine rose to 1.5 mg/dl 6 h following treatment and reached 4.5 mg/dl on day +3. The patient became oliguric with urine output of only 25 ml/day despite aggressive diuretic treatment. On day +3, the serum LDH increased to 9761 U/l, phosphate to 8.8 mg/dl, and uric acid to 15 mg/dl. A diagnosis of rituximab-induced TLS was made, and the patient was treated with IV hydration, allopurinol, and urine alkalinization. The patient refused hemodialysis. Renal function gradually recovered, and serum creatinine and urine output were normal on day +14. The patient later received the remaining 3 planned doses of rituximab uneventfully while treated with allopurinol and hydration. Repeat CT scan of chest, abdomen, and pelvis 1 month after the first dose of rituximab showed complete remission.

CASE TWO

A 76-year-old female had B-cell CLL for 19 years. One year ago, for progressive fatigue and lymphocytosis, she was treated with fludarabine. She had a good response but developed autoimmune hemolysis that failed to respond to corticosteroids and splenectomy but stabilized with IV immunoglobulin. Her lymphocytosis progressed with WBC 907 × 10^9/l. Her performance status declined to 30%. Twelve hours after a single dose of 375 mg/m^2 rituximab was given, her serum LDH rose from 477 to 2538, the phosphate rose to 5.5, and the bicarbonate fell from 19 to 11, associated with Kussmaul respiration. TLS was diagnosed, and hemodialysis was started. Her WBC decreased to 460 × 10^9/l the next day and 34.3 × 10^9/l at day +6. However, her overall condition continued to deteriorate, and she died of sepsis 7 days after rituximab treatment.

DISCUSSION

TLS resulting from effective chemotherapy has been extensively reported in patients with rapidly proliferative hematopoietic malignancies, such as lymphomas and leukemias [10–12], and in patients with solid tumors [13,14]. TLS induced by immunotherapy, on the other hand, is less well appreciated and clinical reports are scanty. We conducted a Medline search regarding immunotherapy-induced TLS (Table I) and found only four reported cases [6,15–17]. Among the six cases presented in the table (including two cases from this report), only rituximab and leukocyte A interferon caused TLS when they were used alone as a monotherapy [6,15].

The patients described in this paper exhibited TLS with elevated phosphate, uric acid, and LDH [18] resulting from massive necrosis of lymphoma/leukemia cells and release of the intracellular degradation products soon after administration of rituximab therapy. TLS resulting from rituximab treatment has so far only been reported in the patient with CLL [6]. The first case described in this paper represents the first report of rituximab-induced TLS occurring in a patient with NHL. In all the cases being reported [6], TLS induced by rituximab has only been observed after the first dose of administration. Patients tolerated the subsequent doses, and no recurrence of TLS has been noted. Interestingly, this side effect profile is very similar to those of other side effects resulting from rituximab treatment [5]. This "up-front" TLS tendency does provide us with an opportunity to respond appropriately by initiation of TLS prophylaxis at the very beginning of rituximab treatment.

Jepsen et al. suggested in their paper that 375 mg/m^2 may be too high for CLL patients who have lymphocyte count over (5–10) × 10^9/l [6]. In their reported case, they have actually predosed the patient with 31.25 mg/m^2 of rituximab (less than 1/10 of the full-dose treatment) prior to giving the rest of the full dose [6]. This predosing with a low dose of rituximab, although not completely preventing TLS, seemed to delay the onset of TLS (24 h after the initiation of the treatment) and attenuate its severity. The results in our patients further support the observation that a dose reduction of rituximab may be necessary for the treatment of the patients who have a high risk to develop TLS. Thus, to reduce the incidence of up-front rituximab-induced TLS in selected patients, it may be worthwhile to consider reducing the dose or dividing the first full dose of rituximab.

Finally, an interesting observation related to our first case, is the effectiveness of rituximab in treating NHL in an immunocompromised AIDS patient. Theoretically, in order to eradicate tumor cells, the host immune system needs to be activated through the binding of rituximab to CD20 antigen on the surface of malignant lymphoma cells, to induce complement-mediated cytolysis, antibody-dependent cellular cytotoxicity, release of cytokines, and induction of cellular apoptosis [3,19]. One concern is that the drug may become less effective in immunocompromised hosts since its attack against tumor

TABLE I. Tumor Lysis Syndrome Induced by Immunotherapies*

Tumor type	Age (sex)	Pretreatment (tumor Load)		Metastasis[a]	Immunotherapy	Onset TLS (h)	Outcome	References
		WBC ($\times 10^9$/l)	LDH					
NHL (diffuse small T cell)	57 (M)	Stage IVA		MLN, C, BM, Cu	Leukocyte A interferon 50 mu/m^2 × 3/wk → 36 mu/m^2 × 3/wk	2 weeks	Improved	Fer [15]
Gastric leiomyosarcoma (intermediate-grade)	66 (M)	s/p gastrectomy	210	L	CY 2 g/m^2 D4 & ALT cells D7[b]	16	Improved	Gold [16]
Melanoma	76 (M)		693	LG, L, SP, PLN, RLN, Cu	MoAbR24 10 mg/m^2 rTNF-α 50 mg/m^2	9	Expired	Minasian [17]
CLL	26 (F)	112 (97% LC)	464	C, BM	Rituxan 375 mg/m^2	24	Improved	Jensen [6]
NHL (high-grade small noncleaved)	41 (M)		3510	Mb, R, TS, LS, CN	Rituxan 375 mg/m^2	6	Improved	Yang
CLL	76 (F)	907 (96% LC)	477		Rituxan 375 mg/m^2	12	Expired	Yang

*(M) = male, (F) = female, LC = lymphocytes, (h) = hours, wk = week, D = day, mu = million units, CY = cyclophosphomide, ALT = autolym phocyte therapy, MoAbR24 = monoclonal antibody R24, rTNF-α = recombinant tumor necrosis factor-α.
[a]Metastasis: S = skull, TS = thoracic spine, LS = lumbar spine, L = liver, LG = lung, SP = spleen, C = cervical, Mb = mandible, R = ribs, CN = CNS, BM = bone marrow, Cu = cutaneous involvement, MLN = mediastinal lymphoadenopathy, RLN = retroperitoneal lymphoadenopathy, PLN = peripheral lymphoadenopathy.
[b]ALT cells were used as a part of the combined chemoimmunotherapy.

cells may be substantially decreased by a defective host immune response. Our patient had a CD4 count of only 107 and was immunocompromised. The fact that TLS occurred right after a single dose of treatment with subsequent tumor regression indicates that rituximab treatment was effective even in an HIV-infected immunocompromised patient. In general, NHL tends to be more aggressive and refractory to standard chemotherapy in AIDS patients. Thus, effective alternatives are necessary and rituximab may be one of such treatments.

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